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Six-Month Comparison of Coronary Endothelial Dysfunction Associated With Sirolimus-Eluting Stent Versus Paclitaxel-Eluting Stent

Jin Won Kim, MD, PHD, Soon Yong Suh, MD, PHD, Cheol Ung Choi, MD, Jin Oh Na, MD, Eung Ju Kim, MD, PHD, Seung-Woon Rha, MD, PHD, Chang Gyu Park, MD, PHD, Hong Seog Seo, MD, PHD, Dong Joo Oh, MD, PHD

Seoul, Republic of Korea

Objectives This study was designed to investigate whether endothelial dysfunction is related to drug-eluting stent (DES) implantation at 6 months after stenting.

Background Current available DES could delay vessel healing and subsequently impair endothelial function.

Methods Endothelial function was estimated at 6-month follow-up in 75 patients (31 men, mean age 62.1 years) with a DES (39 sirolimus-eluting stents [SES], 36 paclitaxel-eluting stents [PES]), and 10 patients with a bare-metal stent (BMS) to the left anterior descending artery, by incremental acetylcholine (Ach) infusion (20 μg/min, 50 μg/min, 100 μg/min) and nitrate (200 μg/min) into the left coronary ostium. Vascular responses were quantitatively measured in arterial segments 5 mm proximal and distal to DES and compared with corresponding segments in the BMS group and midsegments in the left circumflex artery as a reference nonstented artery. All antianginal agents were withheld for at least 72 h before coronary angiography.

Results Greater vasoconstriction to Ach was observed in both the SES and PES groups than in the BMS group or control segments of left circumflex artery. Vasoconstriction to Ach was more prominent in arterial segments distal to stents in both SES and PES groups compared with those in the BMS group ($p < 0.001$). The degree of vasoconstriction to Ach was similar between the SES and PES groups. Endothelium-independent vasodilatation to nitrate did not differ significantly between the study groups.

Conclusions Abnormal vasoconstriction to Ach was found in the SES and PES groups, especially in arterial segments distal to DES at 6 months after stenting, which suggests that DES has a potential long-term adverse effect on local coronary endothelial dysfunction. (J Am Coll Cardiol Intv 2008;1: 65–71) © 2008 by the American College of Cardiology Foundation

From the Cardiovascular Center, Korea University, Guro Hospital, Seoul, Republic of Korea. This study was supported by a Special Research Grant from Korea University, Seoul (to Dr. Kim).

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Drug-eluting stents (DES), a polymer-based sirolimus or paclitaxel local delivery system from a stent platform, have significantly reduced the occurrence of restenosis (1). However, first-generation DES introduced new problems, such as delayed vessel healing and endothelial dysfunction, and in vitro studies have shown that endothelial function in swine coronary segments incubated with sirolimus is severely impaired (2).

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Recent data obtained in human studies showed that sirolimus-eluting stents (SES) can impair endothelial function over a period of 6 months post-implantation (3,4). More recently, Obata et al. (5) showed that sirolimus was significantly detected in the coronary circulation at 2 weeks after SES implantation and the levels of vascular endothelial growth factor (VEGF), the expression of which could be reduced by sirolimus in vitro (6), was lower in the anterior interventricular vein than in the aortic root. Based on these findings, coating drugs released from DES into the coronary flow could affect the endothelial function in the stented artery selectively.

Abbreviations and Acronyms

Ach = acetylcholine
ANOVA = analysis of variance
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)

In view of the antiproliferative effect of paclitaxel, paclitaxel-eluting stents (PES) could also be associated with endothelial dysfunction. However, although the suggestion that PES are associated with endothelial dysfunction has been made in some reports (7,8), data concerning the effects of PES on coronary endothelial function are lacking. Therefore, in the present study, we investigated whether SES or PES implantation is related to coronary endothelial-dependent and endothelial-independent function at 6 months after DES implantation.

Methods

Patients. From March 2002 to March 2007, 75 DES patients (39 Cypher SES [Johnson & Johnson, New Brunswick, New Jersey], 36 Taxus PES [Boston Scientific, Natick, Massachusetts]) and 10 Driver (Medtronic, Minneapolis, Minnesota) cobalt-based bare-metal stent (BMS) patients who were treated with a single DES for a de novo single lesion of the left anterior descending artery underwent coronary angiography and endothelial function testing at 6-month follow-up. Intravascular ultrasound-guided stenting was performed in 9 SES patients (23%) and 4 PES patients (11%). All patients were prospectively recruited at the Department of Cardiology of the Guro Hospital, Korea University, Seoul. Patients with a ≥50% stenotic lesion except for culprit lesion, a history of acute coronary syndrome or coronary spasm (transient ST-segment elevation at rest with chest pain), symptomatic congestive heart failure, left ventricular dysfunction (ejection fraction <30%), in-stent or in-segment restenosis (>30%, reference diameters <2.5 mm or >4.0 mm, respectively), underlying structural heart disease or other serious medical conditions were excluded. Assessments of conventional cardiovascular risk factors were performed in all cases. All patients received aspirin, clopidogrel, and/or cilostazol as an antiplatelet regimen. Unfractionated heparin (50 IU/kg) was given during percutaneous coronary intervention, and glycoprotein IIb/IIIa inhibitors were used at the physician's discretion. This study was approved by the institutional review board of Korea University. Written informed consent was obtained from all patients before study entry.

Evaluation of endothelial function. All antianginal agents were withheld for at least 72 h before coronary angiography. End-diastolic images for each segment were chosen according to the corresponding points on the electrocardiogram trace and analyzed using the proprietary quantitative coronary angiographic system for the catheterization laboratory and an automated edge detection program (BH-3000, Philips, Best, the Netherlands). Simultaneous biplane projections were acquired in all patients. Two orthogonal views with less foreshortening or without overlapping of side branches were selected and averaged for biplane assessment by 2 blinded expert observers.

Endothelial function tests were performed by infusing incremental doses of acetylcholine (Ach) into the left coronary artery through the Judkins catheter (20 μg, 50 μg, and 100 μg for 1 min, performed at an infusion rate of 5 ml/min); a 5-min interval was allowed between doses. When the maximum tolerable dose was reached, intracoronary bolus injection of nitroglycerin (200 μg) was administered. Angiography was repeated after each dose of Ach, and within 2 min of nitrate administration. Infusions were stopped if severe coronary artery constriction occurred at any Ach dose. Two segments in each study vessel, that is, 5 mm proximal and distal to sites of stenting, were chosen for analysis. These segments were chosen regardless of their vascular responses and were in all cases at sites without angiographically evident disease. For comparison with normal response to Ach, the vasomotor reactivity to Ach and nitrate infusion was estimated in the midsegment of nonstented, left circumflex artery. The pre- and adjunctive post-balloon was applied to a shorter area than stent length to avoid areas subject to balloon injury. Changes in coronary diameter in response to Ach and nitrate coronary infusion were expressed as percent changes versus baseline angiograms.

Interobserver and intraobserver variability for repeated measurements of quantitative coronary angiography in the same recordings of 20 randomly selected patients were

0.060 ± 0.03 mm and 0.020 ± 0.02 mm, respectively. During the procedure, blood pressure via guiding catheter and heart rate were continuously monitored.

Statistical analysis. All data are reported as means ± standard deviation. Group demographic data were compared using a 1-way analysis of variance (ANOVA) with a Scheffe test for multiple comparisons for continuous variables, or Kruskal-Wallis ANOVA on ranks followed by the Dunn test for categorical variables. Changes in coronary diameters in response to drug infusions were compared between groups using ANOVA for repeated measurements and followed by post-hoc testing with a Scheffe test for multiple comparisons whenever the general test was significant. Binary variables were analyzed by the Fisher exact test. Changes in mean luminal diameter to maximal Ach dose were compared using 1-way ANOVA with post-hoc (Scheffe) test. For within-group comparisons such as changes in proximal versus distal sites, the paired Student *t* test was used. Statistical significance was accepted at $p < 0.05$. Commercially available computer software (SPSS version 11.0, SPSS Inc., Chicago, Illinois) was used for all analyses.

Results

The baseline characteristics of the 75 DES (56 men, mean age 54.7 years), and 10 BMS (6 men, mean age 60.7 years) patients are shown in Table 1. A total of 39 SES and 36 PES patients were enrolled. There were no differences in age, gender, left ventricular function, hemodynamic variables, or risk factors among the SES, PES, and BMS groups (Table 1).

Angiographic analysis—endothelial dysfunction in the DES and BMS groups. No differences were observed between the PES, SES, and BMS groups in terms of reference segment diameter proximal and distal to the stents (Table 2). The proportions of subjects that achieved a maximal Ach dose were similar among the SES, PES, and BMS groups (84.4% vs. 82.3% vs. 100%, respectively).

Figure 1 shows the typical vasoreactivity in response to Ach infusion in the segments to DES compared with that of BMS or corresponding segments of the left circumflex artery as a reference nonstented artery. After incremental Ach infusion, sites proximal to DES showed a trend toward intense vasoconstriction compared with the BMS group (−18.8 ± 13.6, −14.4 ± 11.9 vs. −3.89 ± 6.79; −21.5 ± 14.9, −19.2 ± 13.9 vs. −5.88 ± 9.90; −24.3 ± 15.6, −23.2 ± 15.7 vs. −6.31 ± 9.63; SES, PES vs. BMS, $p = 0.14$, $p = 0.11$, $p = 0.08$, respectively) (Fig. 2, Table 2). As for sites distal to stents, more significant vasoconstriction occurred in the DES group than in the BMS group (−53.6 ± 14.9, −48.4 ± 11.9 vs. −6.70 ± 5.10; −63.1 ± 16.1, −54.4 ± 13.9 vs. −5.88 ± 14.4; −72.9 ± 11.6, −71.8 ± 15.7 vs. −7.91 ± 20.4; SES, PES vs. BMS, $p < 0.001$, $p < 0.001$, $p < 0.001$ respectively) (Fig. 2, Table 2). The vasomotor reactivity in response to Ach infusion of the left circumflex artery as a reference artery was similar between the SES, PES, and BMS groups (Fig. 2).

Angiographic analysis—endothelial dysfunction in the SES and PES groups. Mean stent diameter and length were not significantly different between the SES and PES groups (Table 2). Regarding vasomotor response to Ach infusion, significant vasoconstrictions to maximal Ach infusion were

Table 1. Baseline Clinical Characteristics

	SES (n = 39)	PES (n = 36)	BMS (n = 10)	p Value*
Age, yrs	63.0 ± 9.5	63.2 ± 10.3	60.7 ± 8.8	0.68
Gender (male, %)	22 (56.4)	19 (52.8)	6 (60.0)	0.55
EF (%)	51.4 ± 8.1	50.3 ± 7.9	52.3 ± 6.18	0.67
Systolic blood pressure (mm Hg)	134 ± 14	129 ± 12	128 ± 14	0.54
Diastolic blood pressure (mm Hg)	86 ± 12	82 ± 9	78 ± 10	0.59
Heart rate (beats/min)	78 ± 5	82 ± 4	84 ± 6	0.57
Underlying disease				
HTN	16 (41.0)	15 (41.6)	5 (50.0)	0.56
DM	7 (17.9)	7 (19.4)	2 (20.0)	0.43
Smoking	8 (20.5)	9 (25.0)	2 (20.0)	0.52
Obesity (BMI >25 kg/m^2)	7 (17.9)	9 (25.0)	2 (20.0)	0.46
Hyperlipidemia	8 (20.5)	8 (22.2)	3 (30.0)	0.33
Family history of CVD	13 (33.3)	11 (30.5)	2 (20.0)	0.37
Medications				
Statin	25 (64.1)	23 (63.8)	7 (58.3)	0.47
ARB/ACEI	12 (30.7)	9 (25.0)	4 (33.3)	0.38

*The p values relate to differences between the 3 groups of patients using analysis of variance: 1) SES group; 2) PES group; 3) BMS group.

ARB/ACEI = angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; BMI = body mass index; BMS = bare-metal stent; CVD = cardiovascular disease; DM = diabetes mellitus; EF = ejection fraction; HTN = hypertension; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

Table 2. Comparison of the Angiographic Changes Among SES, PES, and BMS

	SES (n = 39)	PES (n = 36)	BMS (n = 10)	p Value*
Lesion characteristics				
Diameter stenosis, %	80.3 ± 4.5	76.8 ± 3.9	75.9 ± 6.6	0.78
Lesion length, mm	20.5 ± 6.6	21.1 ± 7.2	18.2 ± 5.2	0.67
Mean stent length, mm	23.3 ± 6.0	24.6 ± 6.8	23.3 ± 8.3	0.73
Stent deployment pressure, mm Hg	13.8 ± 1.1	13.1 ± 1.4	13.1 ± 1.4	0.75
Mean stent diameter	2.96 ± 0.33	2.80 ± 0.37	3.06 ± 0.34	0.36
Proximal to stent				
Reference diameter, mm	3.08 ± 0.11	2.80 ± 0.37	3.16 ± 0.31	0.42
Diameter change to maximal Ach, mm	−0.56 ± 0.73	−0.47 ± 0.64	−0.12 ± 0.26	0.11
Diameter change to maximal Ach, %	−24.7 ± 16.8	−23.4 ± 15.7	−6.23 ± 8.49	0.09
Diameter change to nitrate, mm	0.42 ± 0.48	0.62 ± 0.53	0.51 ± 0.47	0.29
Diameter change to nitrate, %	13.2 ± 13.6	20.2 ± 18.3	14.05 ± 13.8	0.33
Distal to stent				
Reference diameter, mm	2.90 ± 0.48	2.54 ± 0.64	2.60 ± 0.33	0.15
Diameter change to maximal Ach, mm	−2.08 ± 0.18	−1.75 ± 0.12	−0.47 ± 0.23	0.004
Diameter change to maximal Ach, %	−70.9 ± 11.5	−68.7 ± 12.1	−21.6 ± 4.04	<0.001
Diameter change to nitrate, mm	0.55 ± 0.52	0.84 ± 0.80	0.56 ± 0.48	0.24
Diameter change to nitrate, %	18.6 ± 17.8	23.2 ± 27.8	17.21 ± 15.12	0.21

*The p values relate to differences between the 3 groups of patients using analysis of variance: 1) SES group; 2) PES group; 3) BMS group.
Ach = acetylcholine; other abbreviations as in Table 1.

observed in segments proximal and distal to stents (Fig. 3, Table 2). After incremental Ach infusion, mean coronary diameter changes were similar between SES and PES groups (proximal sites: $p = 0.52$, $p = 0.74$, $p = 0.81$; distal sites: $p = 0.72$, $p = 0.60$, $p = 0.92$; A1, A2, A3 respectively) (Fig. 2). Changes in mean luminal diameter in response to Ach were greater at sites distal to than at sites proximal to stents in both the SES and PES groups ($p < 0.001$) (Figs. 2 and 3, Table 2).

Vasoreactivity in response to nitrate infusion. The DES and BMS groups showed no differences of vasodilation in response to nitrate infusion (Table 2). There were no significant differences of vasodilation between sites proximal and distal to stents ($p = 0.56$) (Table 2).

Discussion

In the present study, the SES and PES groups showed greater vasoconstriction of DES-implanted arteries in response to Ach coronary infusion than the BMS group at corresponding segments. Vasoconstriction to Ach was more prominent in arterial segments distal to DES than in proximal segments in both SES and PES groups, but degrees of vasoconstriction to Ach were similar between these groups. Endothelium-independent vasodilatation to nitrate in the DES group and control subjects did not differ significantly. To the best of our knowledge, this is the first published comparison of SES and PES on long-term endothelial dysfunction.

The advent of DES has drastically reduced angiographic restenosis rates as compared with those of BMS (1). However, despite these considerable benefits, issues related to the safety of DES have attracted increasing attention. Moreover, clinical data and some experimental observations have led to speculation that endothelial impairment and delayed healing might compromise DES safety (4). Endothelial dysfunction is associated with the loss of endothelial vasoprotective factors, such as nitric oxide, and possibly subsequent coronary vasoconstriction (9). Acetylcholine may dilate coronary arteries with intact endothelium by inducing the release of nitric oxide, although paradoxically, it constricts vessels when endothelium is damaged (10). Furthermore, endothelial dysfunction is associated with a thrombogenic vascular milieu because of the absences of various substances that promote endothelial survival and proliferation and inhibit platelet aggregation, leukocyte infiltration, and vascular smooth muscle cell proliferation.

Rapamycin and paclitaxel equally suppress endothelial cell proliferation, and consequently impair endothelial function in vitro (2). Experimentally, more than 80% of the rapamycin in SES is eluted at 28 days post-implantation and almost all at 60 days, whereas paclitaxel in PES showed biphasic kinetics with an initial burst during the first 48 h after stent implantation followed by a slow low-level release over at least 2 weeks (11). A previous preclinical study showed that both SES and PES showed normal vascular healing at 1 month, and endothelial function was recovered (12). However, recent reports have raised concerns that late

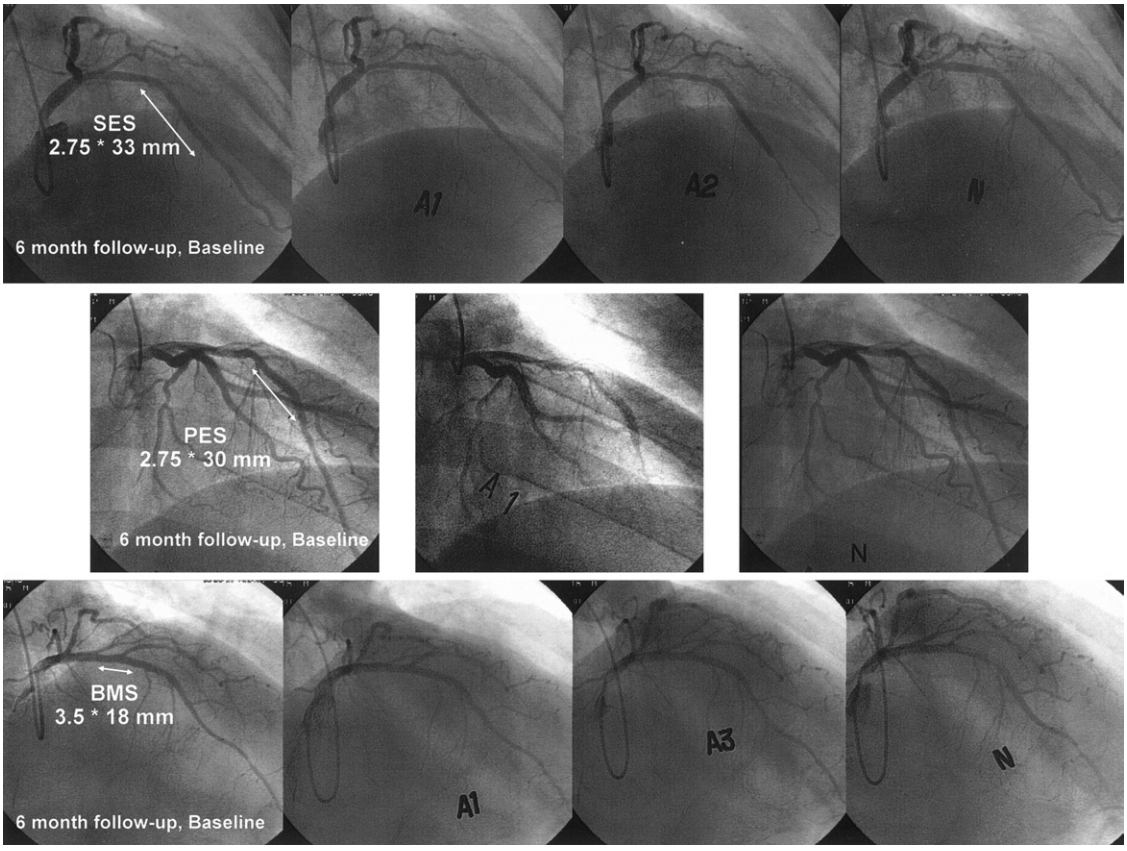

Figure 1. Examples of Coronary Angiogram With Endothelial Function Test at 6 Months After Stent Implantation

Coronary angiogram showed a marked vasoconstriction to incremental acetylcholine infusion, in particular in the segment distal to sirolimus-eluting stent (SES) **(upper panel)** and paclitaxel-eluting stent (PES) **(middle panel)** compared with those of bare-metal stent (BMS) **(lower panel)** or midsegments of the left circumflex artery as a reference nonstented artery.

stent thrombosis is steady, with no evidence of diminution after 3 years of follow-up for SES and PES (13). A morphologic autopsy study showed delayed arterial healing and poor re-endothelialization after DES as compared with BMS over similar durations (14). Considering the antithrombotic role of endothelial cells, endothelial dysfunction after DES implantation might follow a more protracted course in humans than in animals. Although human data regarding the effects of SES and PES on endothelial regeneration are lacking, some case reports have described life-threatening coronary artery spasm after SES or PES implantation (7,15). Recently, Hofma et al. (3) showed that SES implantation is associated with endothelial-dependent vasomotor responses in segments distal to SES compared with BMS 6 months after stent implantation. Togni et al. (16) described a similar phenomenon, namely, exercise-induced paradoxical vasoconstriction of segments adjacent to SES. However, specific information on PES is lacking. A more recent study by Togni et al. (8) showed paradoxical vasoconstriction during exercise in the persistent region to the PES. In the present study, the intense vasoconstrictions to Ach were observed equally for PES and SES as compared with those of BMS. In contrast to animal data, it is uncertain why endothelial dysfunction remains unchanged at 6 months after DES implantation. Despite a lack of data from animal studies, differences in endothelial healing between animals and humans could be caused by the different growth characteristics of their endothelial cells, as was suggested by Kipshidze et al. (17). Both rapamycin and paclitaxel are hydrophobic, and therefore they can easily penetrate vessel walls, which leads to longer drug retention in arterial tissues (18). In line with previous reports, our data show that vasoconstriction to Ach is more prominent in arterial segments distal to rather than proximal to DES in both SES and PES groups. Serry and Penny (19) suggested that a loaded drug may diffuse into the vasa vasorum and consequently influence distal dysfunction. This tentative explanation remains to be elucidated.

In terms of possible confounding factors related to the procedure, high-pressure ballooning with noncompliant

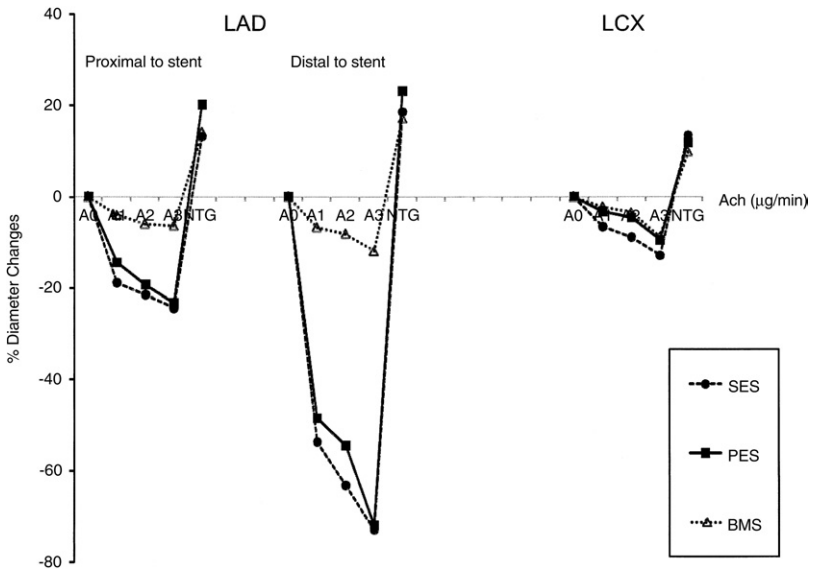

Figure 2. Comparative Analysis of Mean Percent Changes of Coronary Diameter in Response to Incremental Ach and Nitrate Infusion at 6 Months After Stent Implantation

Sites proximal and distal to DES showed a greater vasoconstriction in the DES group than in the BMS group or corresponding segments of the left circumflex artery (LCX) as a reference artery. Mean coronary diameter changes were similar in the SES and PES groups. Ach = acetylcholine; LAD = left anterior descending coronary artery; other abbreviations as in Figure 1.

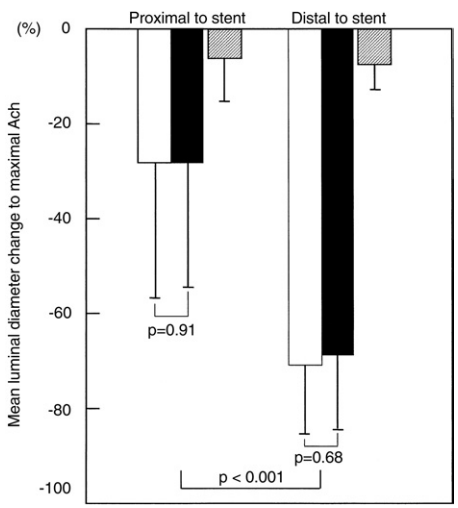

Figure 3. Comparative Analysis of Mean Percent Changes of Coronary Diameter in Response to Maximal Ach at 6 Months After Stent Implantation

Significant vasoconstrictions to maximal Ach infusion were observed in the segments distal to DES compared with those of BMS. Mean coronary diameter changes were similar between SES and PES. Changes in mean luminal diameter in response to Ach were greater at distal than proximal sites to stents in both the SES and PES groups. **Open bars** = SES; **solid bars** = PES; **hatched bars** = BMS. Abbreviations as in Figures 1 and 2.

balloons could have caused arterial wall injury and affected endothelial function. In the present study, pre-ballooning was performed in all cases and adjunctive ballooning in 75% of cases. However, the balloons used were shorter than the stents, and thus, balloon injury at distal or proximal sites adjacent to stent segments was minimized.

Despite strong evidence of delayed endothelial dysfunction associated with DES implantation, it is unclear how long it takes for endothelial function to recover completely. Recently, Togni et al. (8) showed that exercise-induced vasoconstriction adjacent to PES could change and even disappear with time, despite temporal differences between the recoveries of segments proximal and distal to PES. In the future, further study will be required to clarify this issue. In addition, further investigation regarding the relationship between endothelial dysfunction and its contribution to overall DES results including late thrombosis will be warranted.

Study limitations. Several important limitations of this study should be mentioned. First, we could not perform a pre-interventional endothelial function test, and therefore, individual variations in endothelial function may have influenced our results. Second, intravascular ultrasound was available in only some DES patients, and therefore the effects of plaque burden or angiographically undetected edge dissection on coronary endothelial function could not be completely excluded (20). Finally, the degree of vasoconstriction observed in the present study was more pronounced than that described in previous studies. The effects

of Ach on coronary endothelial function are known to be dependent on ethnicity, and Asians show a higher degree of coronary vasoconstriction in response to Ach infusion than Caucasians (21,22). All subjects enrolled in the present study were Koreans, and thus further work is required to ascertain differences in coronary endothelial response to Ach in DES patients by race. To overcome the previously mentioned limitations and answer previously cited questions, a well-designed comparative prospective study on pre- and post-intervention endothelial function for DES versus BMS should be considered. In addition, to clarify the clinical relevance of DES-related endothelial dysfunction, long-term follow-up is required.

Conclusions

This study provides in vivo evidence that both SES and PES can impair endothelial function and that their effects are demonstrably present at 6 months after implantation, especially in arterial segments distal to DES at 6 months post-stenting. Our results suggest that DES have long-term adverse effects on local coronary endothelial function. In addition, clinicians should be concerned about the potential risk of spasm after DES implantation in relation to endothelial dysfunction (4,12).

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Reprint requests and correspondence: Dr. Dong Joo Oh, Guro Hospital, Cardiovascular Center, Korea University, 97 Gurodong-Gil, Guro-gu, Seoul, Republic of Korea, 152-703. E-mail: kjwmm@medimail.co.kr.

REFERENCES

1. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. N Engl J Med 2005;353:653–62.
2. Parry TJ, Brosius R, Thyagarajan R, et al. Drug-eluting stents: sirolimus and paclitaxel differentially affect cultured cells and injured arteries. Eur J Pharmacol 2005;524:19–29.
3. Hofma SH, van der Giessen WJ, van Dalen BM, et al. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. Eur Heart J 2006;27:166–70.
4. Fuke S, Maekawa K, Kawamoto K, et al. Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. Circ J 2007;71:220–5.
5. Obata JE, Kitta Y, Takano H, et al. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related coronary artery in patients with acute myocardial infarction. J Am Coll Cardiol 2007;50:1305–9.
6. Guba M, von Breitenbuch, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med 2002;8:128–35.
7. Kim JW, Park CG, Seo HS, et al. Delayed severe multivessel spasm and aborted sudden death after Taxus stent implantation. Heart 2005;91:e15.
8. Togni M, Raber L, Cocchia R, et al. Local vascular dysfunction after coronary paclitaxel-eluting stent implantation. Int J Cardiol 2007;120:212–20.
9. Furchgott RF. The discovery of endothelium-derived relaxing factor and its importance in the identification of nitric oxide. JAMA 1996;276:1186–8.
10. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.
11. Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. Circ Res 2001;88:756–62.
12. Carter AJ, Aggarwal M, Kopia GA, et al. Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Cardiovasc Res 2004;63:617–24.
13. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;24;369:667–78.
14. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. Circulation 2005;112:270–8.
15. Wheatcroft S, Byrne J, Thomas M, et al. Life-threatening coronary artery spasm following sirolimus-eluting stent deployment. J Am Coll Cardiol 2006;47:1911–2.
16. Togni M, Windecker S, Cocchia R, et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 2005;46:231–6.
17. Kipshidze N, Leon MB. Endothelial dysfunction after drug-eluting stent was never predicted in preclinical studies. J Am Coll Cardiol 2006;47:1911.
18. Hwang CW, Wu D, Edelman ER. Physiological transport forces govern drug distribution for stent-based delivery. Circulation 2001;104:600–5.
19. Serry R, Penny WF. Endothelial dysfunction after sirolimus-eluting stent placement. J Am Coll Cardiol 2005;46:237–8.
20. Gordon JB, Ganz P, Nabel EG, et al. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. J Clin Invest 1989;83:1946–52.
21. Pristipino C, Beltrame JF, Finocchiaro ML, et al. Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. Circulation 2000;101:1102–8.
22. Beltrame JF, Sasayama S, Maseri A. Racial heterogeneity in coronary artery vasomotor reactivity: differences between Japanese and Caucasian patients J Am Coll Cardiol 1999;33:1442–52.